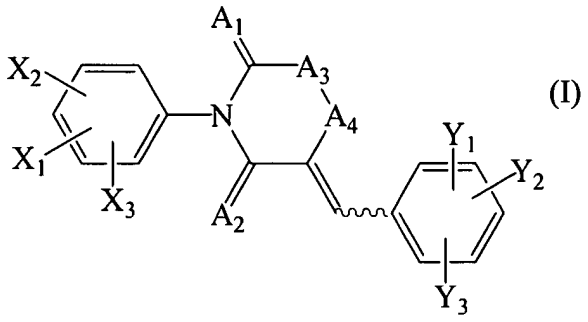
Claims

1. A method of treating a subject having a cystic fibrosis transmembrane conductance regulator (CFTR) protein-mediated condition or symptom, the method comprising administering to the subject a therapeutically effective amount of a compound of formula (I):



(I)

wherein X_1, X_2 and X_3 are independently chosen from hydrogen, an organic group, a halo group, a nitro group, an azo group, a hydroxyl group and a mercapto group; Y_1, Y_2 and Y_3 are independently chosen from hydrogen, an organic group, a halo group, a nitro group, an azo group, a hydroxyl group and a mercapto group; A_1 and A_2 are independently chosen from oxygen and sulfur, A_3 is chosen from sulfur and selenium; and A_4 comprises one or more carbons or heteroatoms and may be present or absent; or a pharmaceutically acceptable derivative thereof, as an individual stereoisomer or a mixture thereof.

2. The method of claim 1, wherein the condition or symptom is associated with aberrantly increased intestinal secretion.

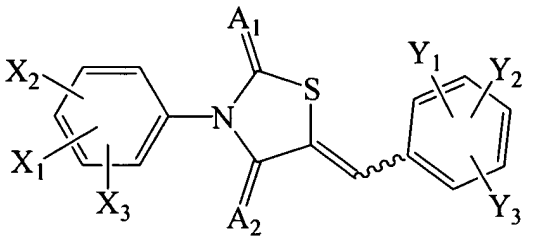
3. The method of claim 2, wherein the condition or symptom is secretory diarrhea.

4. The method of claim 1, wherein the compound of formula (I) is a compound where A_4 is absent, A_1 and A_3 are each sulfur, and A_2 is oxygen, *i.e.*, a 3-aryl-5-arylmethylene-2-thioxo-4-thiazolidinone.

5. The method of claim 1, wherein the compound of formula (I) is chosen from: 3-[(3-trifluoromethyl)phenyl]-5-[(4-nitrophenyl)methylene]-2-thioxo-4-thiazolidinone; 3-[(3-trifluoromethyl)phenyl]-5-[(4-oxycarboxyphenyl)methylene]-2-thioxo-4-thiazolidinone; 3-[(3-

trifluoromethyl)phenyl]-5-[(4-carboxyphenyl)methylene]-2-thioxo-4-thiazolidinone; 3-[(3-trifluoromethyl)phenyl]-5-[(3,4-dihydroxyphenyl)methylene]-2-thioxo-4-thiazolidinone; 3-[(3-trifluoromethyl)phenyl]-5-[(3,5-dibromo-4-hydroxyphenyl)methylene]-2-thioxo-4-thiazolidinone; and 3-[(3-trifluoromethyl)phenyl]-5-[(3-bromo-4-hydroxy-5-nitrophenyl)methylene]-2-thioxo-4-thiazolidinone.

6. The method of claim 1, wherein the compound of formula (I) is a compound of formula (Ia):



(Ia)

wherein X_1, X_2 and X_3 are independently chosen from hydrogen, an organic group, a halo group, a nitro group, an azo group, a hydroxyl group and a mercapto group; Y_1, Y_2 and Y_3 are independently chosen from hydrogen, an organic group, a halo group, a nitro group, an azo group, a hydroxyl group and a mercapto group; and A_1 and A_2 are independently chosen from oxygen and sulfur.

7. The method of claim 6, wherein X_1 is an electron-withdrawing group.

8. The method of claim 7, wherein X_1 is selected from the group consisting of a perfluoroalkyl group and a fluoro group.

9. The method of claim 8, wherein Y_2 is chosen from alkyl, hydroxyl, carboxyl, nitro, carbonate, carbamate, alkoxy, alkylcarbonyl, and a halo group.

10. The method of claim 7, wherein X_1 is a 3-trifluoromethyl group.

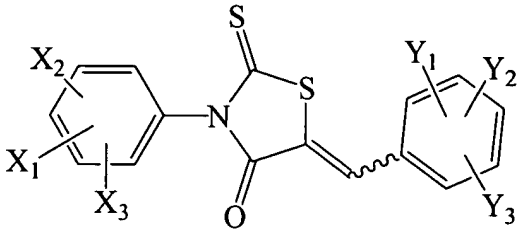
11 The method of claim 6, wherein Y_2 is a hydroxyl group.

12. The method of claim 11, wherein Y_1 is a hydroxyl group.

13. The method of claim 11, wherein Y_1 is a bromo group.

14. The method of claim 11, wherein Y_3 is a nitro group.

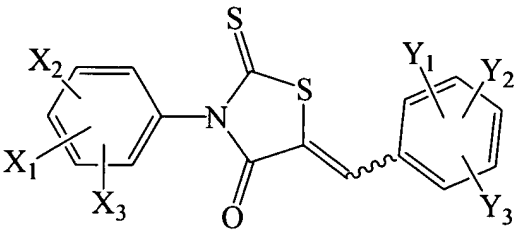
15. The method of claim 1, wherein the compound of formula (I) is a compound of formula (Ib):



(Ib)

wherein X_1, X_2 and X_3 are independently chosen from hydrogen and an organic group;and Y_1, Y_2 and Y_3 are independently chosen from hydrogen and an organic group.

16. The method of claim 1, wherein the compound of formula (I) is a compound of formula (Ib):



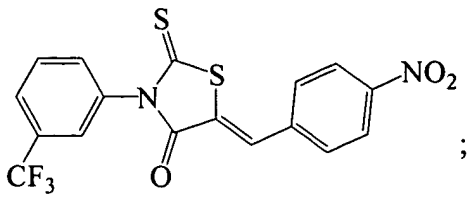
(Ib)

wherein at least one of X_1, X_2 and X_3 is an electron-withdrawing group; and Y_1, Y_2 and Y_3 are independently chosen from hydrogen, alkyl, hydroxyl, carboxyl, nitro, carbonate, carbamate, alkoxy, alkylcarbonyl, and a halo group.

17. The method of claim 16, wherein X_1 is a trifluoromethyl group.

18. The method of claim 17, wherein X_1 is a 3-trifluoromethyl group.

19. The method of claim 1, wherein the compound of formula (I) is chosen from: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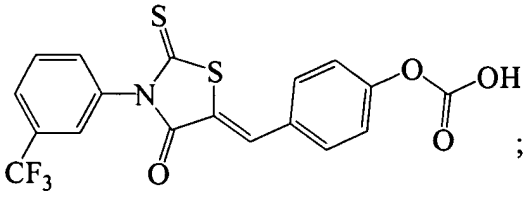
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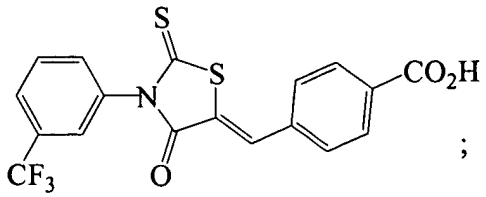
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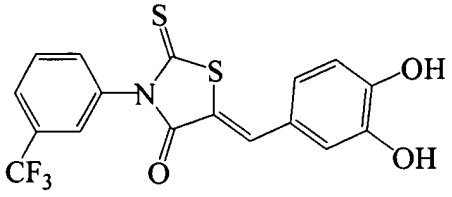
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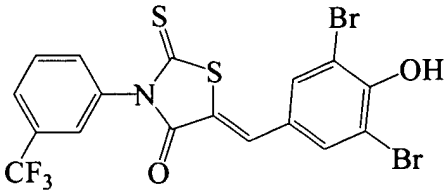
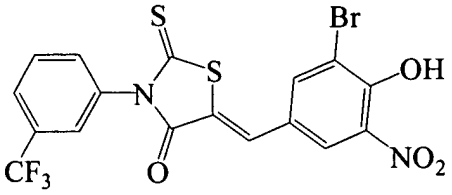

; and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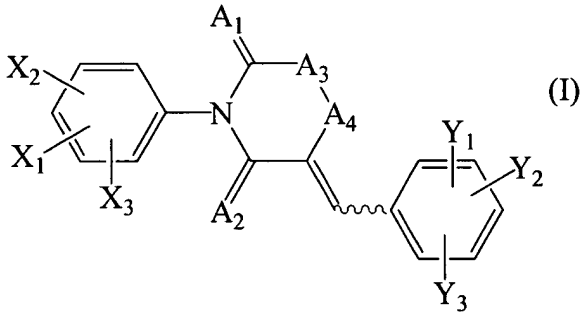
20. A method for inhibiting the activity of cystic fibrosis transmembrane conductance regulator protein in a cell of a subject, comprising contacting the cell with a compound of formula (I):

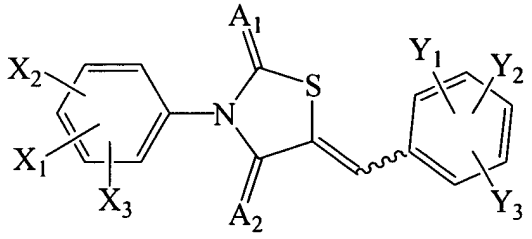

(I)

wherein X_1, X_2 and X_3 are independently chosen from hydrogen, an organic group, a halo group, a nitro group, an azo group, a hydroxyl group and a mercapto group; Y_1, Y_2 and Y_3 are independently chosen from hydrogen, an organic group, a halo group, a nitro group, an azo group, a hydroxyl group and a mercapto group; A_1 and A_2 are independently chosen from oxygen and sulfur, A_3 is chosen from sulfur and selenium; and A_4 comprises one or more carbons or heteroatoms and may be present or absent; or a pharmaceutically acceptable derivative thereof, as an individual stereoisomer or a mixture thereof; in an amount sufficient to inhibit CFTR ion transport in the cell.

21. The method of claim 20, wherein the compound of formula (I) is a compound where A_4 is absent, A_1 and A_3 are each sulfur, and A_2 is oxygen, *i.e.*, a 3-aryl-5-arylmethylene-2-thioxo-4-thiazolidinone.

22. The method of claim 21, wherein the compound of formula (I) is chosen from: 3-[(3-trifluoromethyl)phenyl]-5-[(4-nitrophenyl)methylene]-2-thioxo-4-thiazolidinone; 3-[(3-trifluoromethyl)phenyl]-5-[(4-oxycarboxyphenyl)methylene]-2-thioxo-4-thiazolidinone; 3-[(3-trifluoromethyl)phenyl]-5-[(4-carboxyphenyl)methylene]-2-thioxo-4-thiazolidinone; 3-[(3-trifluoromethyl)phenyl]-5-[(3,4-dihydroxyphenyl)methylene]-2-thioxo-4-thiazolidinone; 3-[(3-trifluoromethyl)phenyl]-5-[(3,5-dibromo-4-hydroxyphenyl)methylene]-2-thioxo-4-thiazolidinone; and 3-[(3-trifluoromethyl)phenyl]-5-[(3-bromo-4-hydroxy-5-nitrophenyl)methylene]-2-thioxo-4-thiazolidinone.

23. The method of claim 20, wherein the compound of formula (I) is a compound of formula (Ia):



(Ia)

wherein X_1, X_2 and X_3 are independently chosen from hydrogen, an organic group, a halo group, a nitro group, an azo group, a hydroxyl group and a mercapto group; Y_1, Y_2 and Y_3 are independently chosen from hydrogen, an organic group, a halo group, a nitro group, an azo group, a hydroxyl group and a mercapto group; and A_1 and A_2 are independently chosen from oxygen and sulfur.

24. The method of claim 23, wherein X_1 is an electron-withdrawing group.

25. The method of claim 24, wherein X_1 is chosen from a perfluoroalkyl group and a fluoro group.

26. The method of claim 24, wherein X_1 is a 3-trifluoromethyl group.

27. The method of claim 23, wherein Y_2 is chosen from alkyl, hydroxyl, carboxyl, nitro, carbonate, carbamate, alkoxy, alkylcarbonyl, and halo groups.

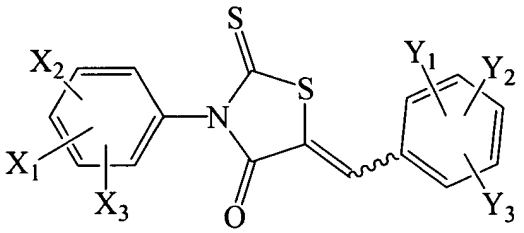
28. The method of claim 23, wherein Y_2 is a hydroxyl group.

29. The method of claim 28, wherein Y_1 is a hydroxyl group.

30. The method of claim 28 wherein Y_1 is a bromo group.

31. The method of claim 28, wherein Y_3 is a nitro group.

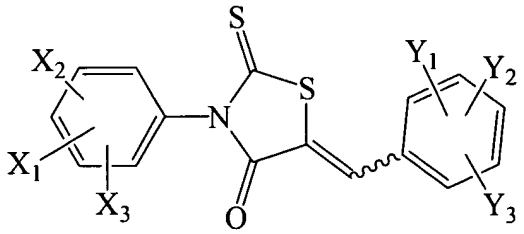
32. The method of claim 20, the compound of formula (I) is a compound of formula (Ib):



(Ib)

wherein X_1, X_2 and X_3 are independently chosen from hydrogen and an organic group; and Y_1, Y_2 and Y_3 are independently chosen from hydrogen and an organic group.

33. The method of claim 20, wherein the compound of formula (I) is a compound of formula (Ib):



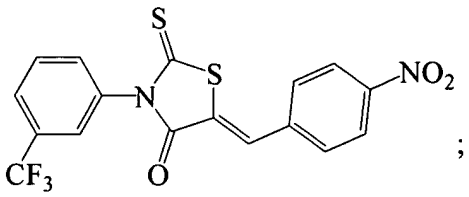
(Ib)

wherein at least one of X_1, X_2 and X_3 is an electron-withdrawing group; and Y_1, Y_2 and Y_3 are independently chosen from hydrogen, alkyl, hydroxyl, carboxyl, nitro, carbonate, carbamate, alkoxy, alkylcarbonyl, and a halo group.

34. The method of claim 33, wherein X_1 is a trifluoromethyl group.

35. The method of claim 34, wherein X_1 is a 3-trifluoromethyl group.

36. The method of claim 20, wherein the compound of formula (I) is chosen from: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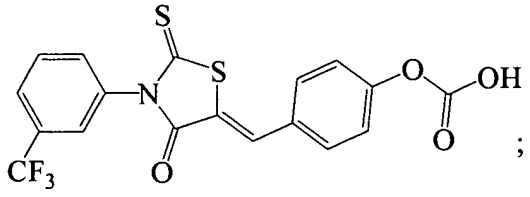
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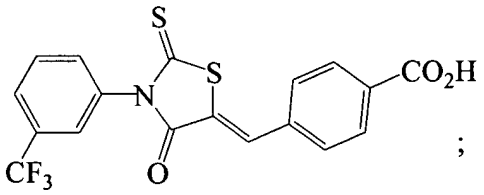
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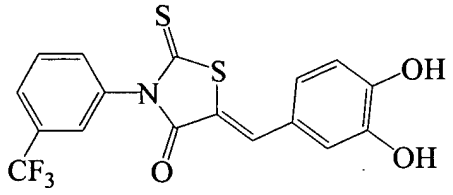
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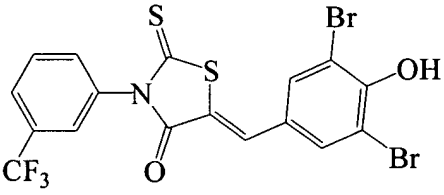
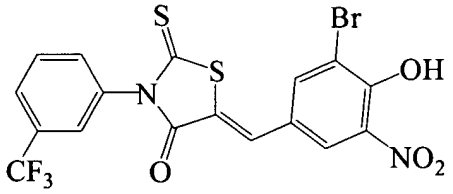

; and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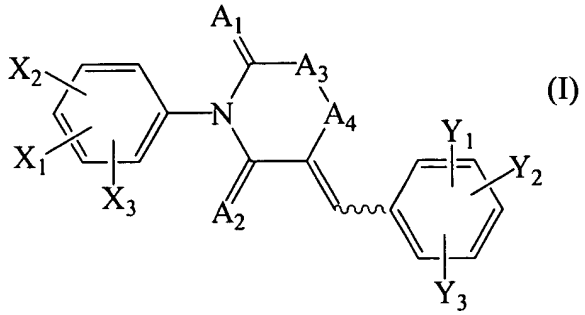
37. The method of claim 20, wherein contacting the cell comprises ingesting, by the subject, the compound of formula (I).

38. The method of claim 37, wherein the ingesting further comprises ingesting a pharmaceutically acceptable carrier together with the compound of formula (I).

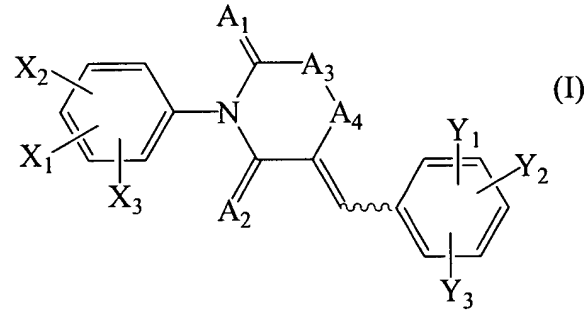
39. A method for inhibiting the activity of cystic fibrosis transmembrane conductance regulator protein in a cell in an *in vivo* assay, comprising contacting the cell with a compound of formula (I):



(I)

wherein X_1, X_2 and X_3 are independently chosen from hydrogen, an organic group, a halo group, a nitro group, an azo group, a hydroxyl group and a mercapto group; Y_1, Y_2 and Y_3 are independently chosen from hydrogen, an organic group, a halo group, a nitro group, an azo group, a hydroxyl group and a mercapto group; A_1 and A_2 are independently chosen from oxygen and sulfur, A_3 is chosen from sulfur and selenium; and A_4 comprises one or more carbons or heteroatoms and may be present or absent; or a pharmaceutically acceptable derivative thereof, as an individual stereoisomer or a mixture thereof, in an amount sufficient to inhibit CFTR ion transport in the cell.

40. A method for producing the cystic fibrosis (CF) phenotype in a non-human animal, wherein the method comprises administering to the non-human animal a compound of formula (I):



(I)

wherein X_1, X_2 and X_3 are independently chosen from hydrogen, an organic group, a halo group, a nitro group, an azo group, a hydroxyl group and a mercapto group; Y_1, Y_2 and Y_3 are independently chosen from hydrogen, an organic group, a halo group, a nitro group, an azo group, a hydroxyl group and a mercapto group; A_1 and A_2 are independently chosen from

oxygen and sulfur, A_3 is chosen from sulfur and selenium; and A_4 comprises one or more carbons or heteroatoms and may be present or absent; or a pharmaceutically acceptable derivative thereof, as an individual stereoisomer or a mixture thereof; in an amount sufficient to induce the cystic fibrosis (CF) phenotype in the non-human animal.

41. A method of treating a subject having a condition associated with aberrant ion transport by cystic fibrosis transmembrane conductance regulator (CFTR) in a subject, the method comprising:

administering to the subject an efficacious amount of a thiazolidinone compound;

wherein CFTR ion transport is inhibited and the condition is treated.

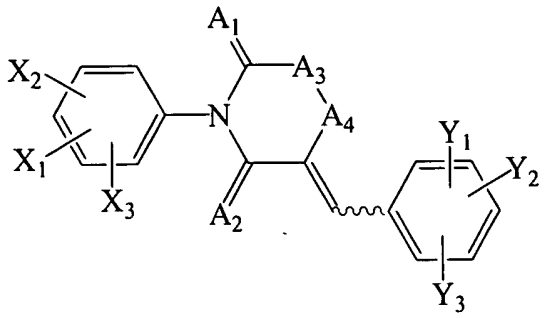
42. The method of claim 41, wherein the aberrantly increased CFTR ion transport is associated with diarrhea.

43. The method of claim 42, wherein the diarrhea is secretory diarrhea.

44. A pharmaceutical composition comprising a thiazolidinone compound , independently chosen from: 3-[(3-trifluoromethyl)phenyl]-5-[(4-nitrophenyl)methylene]-2-thioxo-4-thiazolidinone; 3-[(3-trifluoromethyl)phenyl]-5-[(4-oxycarboxyphenyl)methylene]-2-thioxo-4-thiazolidinone; 3-[(3-trifluoromethyl)phenyl]-5-[(4-carboxyphenyl)methylene]-2-thioxo-4-thiazolidinone; 3-[(3-trifluoromethyl)phenyl]-5-[(3,4-dihydroxyphenyl)methylene]-2-thioxo-4-thiazolidinone; 3-[(3-trifluoromethyl)phenyl]-5-[(3,5-dibromo-4-hydroxyphenyl)methylene]-2-thioxo-4-thiazolidinone; and 3-[(3-trifluoromethyl)phenyl]-5-[(3-bromo-4-hydroxy-5-nitrophenyl)methylene]-2-thioxo-4-thiazolidinone; and at least one of a pharmaceutically acceptable carrier, a pharmaceutically acceptable diluent, a pharmaceutically acceptable excipient and a pharmaceutically acceptable adjuvant.

45. The composition of claim 44, wherein the composition does not contain detectable dimethyl sulfoxide.

46. A pharmaceutical composition comprising a compound of formula (I):



(I)

wherein X_1, X_2 and X_3 are independently chosen from hydrogen, an organic group, a halo group, a nitro group, an azo group, a hydroxyl group and a mercapto group; Y_1, Y_2 and Y_3 are independently chosen from hydrogen, an organic group, a halo group, a nitro group, an azo group, a hydroxyl group and a mercapto group; A_1 and A_2 are independently chosen from oxygen and sulfur, A_3 is chosen from sulfur and selenium; and A_4 comprises one or more carbons or heteroatoms and may be present or absent; or a pharmaceutically acceptable derivative thereof, as an individual stereoisomer or a mixture thereof,

provided, however, that when:

1) A_4 is absent, A_1 and A_2 are each oxygen, A_3 is sulfur, one of X_1, X_2, and X_3 is trifluoromethyl or chloro in the 4-position and the others of X_1, X_2, and X_3 are each hydrogen, one of Y_1, Y_2, and Y_3 can not be 4-methylpiperazin-1-yl in the 2-position when the remaining others of Y_1, Y_2, and Y_3 are each hydrogen;

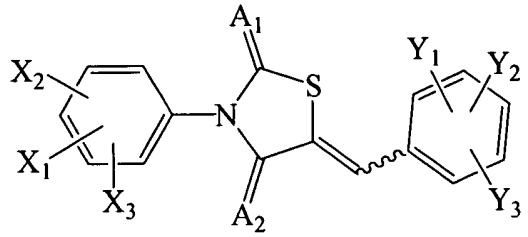
2) A_4 is absent, A_1 and A_3 are each sulfur, A_2 is oxygen, one of X_1, X_2, and X_3 is carboxyl in the 4-position and the others of X_1, X_2, and X_3 are each hydrogen, Y_1, Y_2, and Y_3 can not each be hydrogen;

3) A_4 is absent, A_1 and A_3 are each sulfur, A_2 is oxygen, one of X_1, X_2, and X_3 is hydroxy in the 2-, 3- or 4-position or ethoxy in the 4-position and the others of X_1, X_2, and X_3 are each hydrogen, one of Y_1, Y_2 and Y_3 is hydrogen, and another of Y_1, Y_2 and Y_3 is hydroxy or methoxy in the 4-position, the remaining one of Y_1, Y_2 and Y_3 can not be methoxy in the 3-position; and

4) A_4 is absent, A_1 and A_3 are each sulfur, A_2 is oxygen, one of X_1, X_2, and X_3 is methyl in the 4-position and another of X_1, X_2, and X_3 is chloro in the 3-position, one of Y_1, Y_2 and Y_3 is methoxy in the 4-position, the remaining others of Y_1, Y_2 and Y_3 can not each be hydrogen;

and at least one of a pharmaceutically acceptable carrier, a pharmaceutically acceptable diluent, a pharmaceutically acceptable excipient and a pharmaceutically acceptable adjuvant.

47. The composition of claim 46, wherein the compound of formula (I) is a compound of formula (Ia):



(Ia)

wherein X_1, X_2 and X_3 are independently chosen from hydrogen, an organic group, a halo group, a nitro group, an azo group, a hydroxyl group and a mercapto group; Y_1, Y_2 and Y_3 are independently chosen from hydrogen, an organic group, a halo group, a nitro group, an azo group, a hydroxyl group and a mercapto group; and A_1 and A_2 are independently chosen from oxygen and sulfur.

48. The composition of claim 47, wherein X_1 is an electron-withdrawing group.

49. The composition of claim 48, wherein X_1 is chosen from a perfluoroalkyl group and a fluoro group.

50. The composition of claim 47, wherein Y_2 is chosen from alkyl, hydroxyl, carboxyl, nitro, carbonate, carbamate, alkoxy, alkylcarbonyl, and a halo group.

51. The composition of claim 47, wherein X_1 is a 3-trifluoromethyl group.

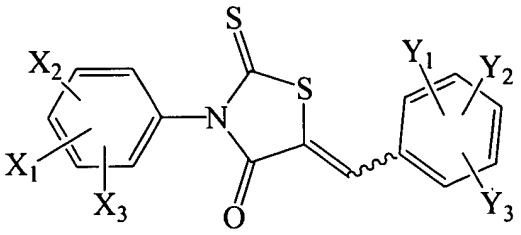
52. The composition of claim 47, wherein Y_2 is a hydroxyl group.

53. The composition of claim 52, wherein Y_1 is a hydroxyl group.

54. The composition of claim 52, wherein Y_1 is a bromo group.

55. The composition of claim 54, wherein Y_3 is a nitro group.

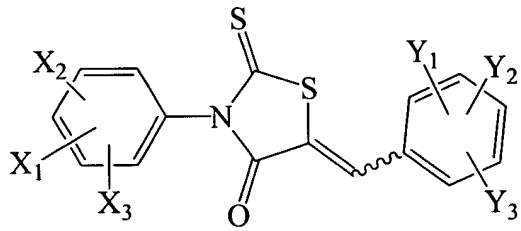
56. The composition of claim 46, wherein the compound of formula (I) is a compound of formula (Ib):



(Ib)

wherein X_1, X_2 and X_3 are independently chosen from hydrogen and an organic group; andY_1, Y_2 and Y_3 are independently chosen from hydrogen and an organic group.

57. The composition of claim 46, wherein the compound of formula (I) is a compound of formula (Ib):



(Ib)

wherein at least one of X_1, X_2 and X_3 is an electron-withdrawing group; and Y_1, Y_2 and Y_3 are independently chosen from hydrogen, alkyl, hydroxyl, carboxyl, nitro, carbonate, carbamate, alkoxy, alkylcarbonyl, and a halo group.

58. The composition of claim 57, wherein X_1 is a trifluoromethyl group.

59. The composition of claim 57, wherein X_1 is a 3-trifluoromethyl group.

60. The composition of claim 46, wherein the composition does not contain detectable dimethyl sulfoxide.

61. A non-human animal having a cystic fibrosis transmembrane conductance regulator (CFTR) deficiency, wherein the deficiency is produced by administration of a thiazolidinone compound to the animal in an amount effective to inhibit CFTR ion transport.

62. The non-human animal of claim 61, wherein the animal is a mammal.

63. The non-human animal of claim 62, wherein the mammal is a non-human primate, rodent, ungulate, or avian.

64. The non-human animal of claim 61, wherein the animal has a phenotype similar to cystic fibrosis.